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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PURDY, KYLE A	

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1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,296	HAAS ET AL.	
	Examiner	Art Unit	
	Kyle Purdy	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2006 and 04 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 17-22* is/are pending in the application.

4a) Of the above claim(s) *17-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 sheet (06/23/2006)*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Restriction Requirement

1. Applicant's election with traverse of Group I encompassing claims 1-15 in the reply filed on January 4, 2008 is acknowledged. The traversal is on the ground(s) that Groups I-III are related as collodial preparations comprising cationic colloidal nanoparticles and an active agent, methods of making and methods of using the nanoparticles and that the search over one group of invention would result in finding pertinent art for the other groups of invention. Finally it would not be a serious search burden on the Patent Office to search and examine all groups. This is not found persuasive because the reference of Unger et al. ('Unger) teaches loading preformed micelles with a biologically active agent involving the dehydration and rehydration of liposome vesicles followed by loading with active agents. Also, the inventions do not reflect a single invention because they employ different components, different steps and have different modes of operation in order to achieve their objectives. Different areas of search would be necessary in order to determine whether they are distinguished over the prior art. Hence, a lack of unity is deemed proper and is made FINAL.

2. Claims 17-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 4, 2008.

3. Claims 1-15 and 17-22 are pending, claims 17-22 are withdrawn and claims 1-15 are presented for examination on the merits. The following rejections are made.

Applicants' Invention

4. A method of producing a colloidal preparation comprising cationic colloidal nanoparticles and an active agent comprising the steps of a) providing an active agent [camptothecin and analogs thereof]; b) providing empty cationic nanoparticles comprising a cationic component; and c) incubating said active agent of step a) with the empty cationic colloidal nanoparticles of step b) in an aqueous medium [between 10 minutes to about 6 hours at about 4 to 25°C] to cause sufficient loading of the nanoparticles wherein step c) is performed without further steps such as self-assembly. The cationic nanoparticles may be selected from micelles, liposomes and nanocapsules, which may be solid or an aqueous dispersion, wherein the cationic component is a cationic amphiphile, polymer or a cationic lipid.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. **Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

7. Claim 1 recites the limitation, "wherein step c) is performed without further steps as a self-assembly process". This renders the claim indefinite because it is unclear as to what limitations are to be encompassed. The phrase "performed without further steps" implies that that the preformed nanoparticle and active agent containing solutions are mixed and that is it, no other steps are carried out on the mixture such as the removal of excess drug or dilution. However, the

recitation of "without further steps as a self-assembly" indicates that the 'further steps' are directed more toward the thermodynamic process of forming the active liposome, which is distinct from the first interpretation. The Examiner is interpreting the claim to be directed toward the latter, wherein 'further steps' means that preformed empty nanoparticles are mixed with drug, rather than mixing free lipid molecules with drug. Clarification is required.

8. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 3 recites the broad recitation "said active agent is present in an amount of about 0.1 mol% to less than about 100 mol%...", and the claim also recites "wherein said active agent is ..... preferably from about 1 mol% to about 50 mol%, more preferably....." which is the narrower statement of the range/limitation.

9. Note, claim 6 is rejected for the same reason as claim 3.

10. Regarding claims 10-13, the terms "particularly" and "preferably" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. **Claims 1, 8-11 and 15 rejected under 35 U.S.C. 102(b) as being anticipated by Huang et al (US 6008202).**

13. Huang et al. ('Huang) discloses the loading of cationic micelles with active agents such as nucleic acids, drugs and proteins (see column 7, lines 43-45). In Example 1 of Huang (see column 18, lines 5-10), it is taught that pRSVL plasmid DNA (active agent) was incubated with cationic liposome at a pH of 7.6 for 7 minutes (see instant claims 1 and 8-11 and 15). The cationic lipid materials used in the liposomes qualify as a cationic amphiphile (see claim 10), cationic lipid (see claim 11) and are necessarily in the form of an aqueous dispersion (see claim 9).

14. Thus, as the limitations of the claims 1, 8-11 and 15 are met by Huang, the claims are anticipated.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. **Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Slater et al. (US 6355268), supported by Cullis et al. (Biochemica at Biophysica Acta, 1997, 1331, 187-211).**

18. Slater et al. ('Slater) is drawn to a composition and a method of making a liposome loaded with a therapeutically effective dose of a topoisomerase I and/or topoisomerase II inhibitor (see abstract). The preferred species of topoisomerase I inhibitors include camptothecin which is a hydrophobic compound that equilibrates between two forms an active lactone form and a less active carboxylate form wherein the equilibration is dependent upon temperature, pH, etc.. The active agents taught by Slater include camptothecin and its analogs, such as SN-38 (see column 8, lines 52-65; see instant claims 4-7). The liposome components include components that readily form vesicles upon contact with water such as lipids, preferably cationic lipids like

1,2-dioleyloxy-3-(trimethylamino) propane (DOTAP) (see column 6, lines 46-55; see instant claims 9-11).

19. The method implemented by Slater requires preparing a cationic liposome solution and a separate topoisomerase I inhibitor (MPE-camptothecin) solution, mixing the two preparations together and rapidly warming to 65°C for 40-50 minutes (see column 21, lines 1-20; see instant claims 4-7 and 12). Slaters final product was placed in a solution which had a pH of 6.5 (see column 21, lines 20-25; see instant claim 15). It is taught that the % encapsulation by this process resulted in 96.4% of the drug successfully being encapsulated (see table in column 21) and the MPE-camptothecin concentration per cationic component in the liposome is roughly 25 mole percent (see table in column 21; see instant claim 3). The composition made by Slater is suitable for immediate delivery into a subject as taught in Example 2 wherein mice are dosed with drug-loaded liposomes immediately following its synthesis (see column 21, lines 60-67; see instant claim 14).

20. Thus, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to use the teaching of Slater with a reasonable expectation of success at arriving at a method of effectively loading empty cationic nanoparticles with active agents like the topoisomerase inhibitor camptothecin, wherein the loading process does not occur via a self-assembly process. The significance of Slater is that it teaches a method for making a pharmaceutically active liposome comprising a cationic lipid and a camptothecin or an analog thereof such as SN-38. With respect to the instant claims recitation that camptothecin is predominately in the carboxylate form would necessarily have to be so as the solution in which the camptothecin is present in is maintained at a physiological pH (i.e. pH ~7.3) which is a pH

where the carboxylate form dominates over the lactone. Such a recitation describing the result of the free compound in solution carries no patentable weight as it is a property inseparable from the compound itself. The major shortcoming of Slater is that upon mixing the liposome solution with the drug solution, the mixture is heated rather than cooled or incubated at low temperatures (25°C). However, the temperature is a result oriented parameter which one ordinarily skilled in the art would be motivated to adjust such that the resulting drug-loaded liposome would contain the maximum amount of camptothecin or analog thereof. The notion that adjusting the temperature during the loading process would be obvious is supported by Cullis et al. ('Cullis).

21. Cullis is a biophysical study drawn to understanding how thermodynamic and physiochemical properties affect drug uptake by preformed lipid vesicles. Figure 5 (A) of Cullis (see page 195) illustrates the effect that temperature has on the liposomes drug loading efficiency. The reference clearly illustrates that temperature is directly related to the uptake of drug by the vesicle, and it follows that one of ordinary skill in the art would be motivated to alter the temperature of the method taught by Slater with the goal of arriving at an optimized method for producing drug loaded vesicles. If the result of such an undertaking was such that the optimum temperature for making the liposomal product was between 6° to 25°C, then that result would not be due to innovation, but rather ordinary skill and common sense. Therefore, the invention as a whole is *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

22. Note, Cullis was cited to show that the temperature was a result oriented parameter which one would readily adjust to optimize the loading conditions.

Conclusion

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kyle A. Purdy whose telephone number is 571-270-3504. The examiner can normally be reached from 9AM to 5PM.

24. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

25. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Kyle Purdy/
Examiner, Art Unit 1611

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